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Epidemiology: Review of published study

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Subject	Neurodevelopmental outcomes following prenatal acetaminophen exposure
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EXECUTIVE SUMMARY

The purpose of this review is to respond to the Division of Nonprescription Drug Products' (DNDP) request for an evaluation of a recent publication in *JAMA Pediatrics* reporting an association between prenatal acetaminophen (APAP) exposure and behavioral problems in childhood. Previous reviews have addressed this topic, which is the subject of Tracked Safety Issue #1355. During the review of this publication, three more new studies of prenatal APAP exposure and neurodevelopmental outcomes were identified; all are covered in this review. In addition, this review recapitulates findings from the 4 older studies covered in previous reviews.

To summarize findings from the four 2016 publications:

- The study by Stergiakouli et al. assessed behavioral problems identified on a parental questionnaire when the children were 7 years of age, and found that prenatal APAP exposure was associated with measures of behavioral difficulties, including hyperactivity.
- The study by Avella-Garcia et al. assessed symptoms of attention deficit hyperactivity disorder (ADHD) and other behavioral problems at age 5, and found that prenatal APAP exposure was associated with more ADHD symptoms and (in males) more autistic symptoms.
- The study by Liew et al. assessed IQ at age 5, finding that IQ was lower in children with prenatal APAP exposure, though more so in the absence of maternal fever; i.e., APAP may have mitigated the effect of maternal fever on IQ.
- The study by Vlenterie et al. assessed a variety of behavioral and developmental outcomes at age 18 months, finding that delayed walking was associated with in utero APAP exposure.

Altogether, 8 observational studies have examined neurodevelopmental outcomes following prenatal APAP exposure, and while the quality of the evidence varied across studies, a total of 7 showed some association with adverse neurodevelopmental outcomes. While some conditions that might lead mothers to take APAP during pregnancy can be associated with neurodevelopmental harms (particularly fever), several of the studies tried to account for this with various strategies, and one study showed an association with APAP exposure that was not present for ibuprofen use. Additionally, the recent publication by Liew et al. suggested some mitigation of the risk of fever by APAP, but found a decrement in IQ when APAP was used by mothers without fever.

With growing evidence for adverse neurodevelopmental outcomes being associated with in utero APAP exposure, even in the absence of proof of a causal relationship, it would be appropriate for FDA to bring this issue to the attention of consumers and health care providers through one of the communication avenues available to the agency. The essential points to communicate would be that current data raise the possibility of neurodevelopmental harm to the fetus from maternal APAP use, that it should be used judiciously during pregnancy, that other analgesics are associated with more definite pregnancy risks, and that APAP may be needed as an antipyretic to reduce risks associated with maternal fever.

With respect to further evaluation of this signal, it may be beneficial to re-consult Pharmacology/Toxicology to ask whether any preclinical models might address any of the expanded spectrum of neurodevelopmental outcomes that have now been associated with prenatal APAP exposure.

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1 INTRODUCTION

The Division of Nonprescription Drug Products (DNDP) requested the Division of Epidemiology 1 (DEPI1) to review a publication in *JAMA Pediatrics*[1] showing an association between prenatal acetaminophen (APAP) exposure and behavioral problems in exposed offspring. We identified 3 more recently published studies of neurodevelopmental outcomes following prenatal APAP exposure, which we also review herein.[2,3,4]

Studies of the behavioral teratogenicity of APAP have been the subject of two previous DEPI-I reviews, on May 15, 2014, by Dr. Lockwood Taylor, and March 18, 2015, by this reviewer. These reviews were part of the evaluation of Tracked Safety Issue #1355. The present review will also summarize previous epidemiologic studies of this potential association.

1.1 BACKGROUND

Acetaminophen is a widely used analgesic and antipyretic available without a prescription. The product is also marketed as a component of combination prescription products. It is widely used during pregnancy; in one U.S. study, 65% of mothers reported taking APAP while they were pregnant.[5] Although it crosses the placenta, APAP is regarded as the analgesic of choice during pregnancy, as aspirin during pregnancy has been associated with perinatal mortality, neonatal hemorrhage, low birth weights, and prolonged labor, [6] while non-steroidal anti-inflammatory drugs can induce premature closure of the ductus arteriosis, and are associated with other complications (such as oligohydramnios, renal dysfunction, and intracranial hemorrhage, among others).[7]

Various studies have examined prenatal factors as risk factors for attention deficit hyperactivity disorder (ADHD).[8] Maternal smoking and alcohol use during pregnancy, prenatal maternal stress, viral rash during pregnancy, low birth weight, polychlorinated biphenyl and lead exposure,[9] paternal smoking during the pregnancy,[10] maternal age,[11] and (relevant with respect to APAP use) maternal urinary tract infection[12] have all been associated with ADHD. Additionally, maternal infection has been associated with autistic spectrum disorders.[13]

A recent systematic review of 46 studies of the effects of fever during pregnancy reported particularly strong evidence for associations with neural tube defects, congenital heart defects, and oral clefts. The authors also reported that in the majority of studies that examined use of antipyretic medication for fever, antipyretics appeared to reduce the risk of the birth defect of interest relative to unmedicated fever.[14] One of the case-control studies cited in that systematic review found that maternal fever (but not maternal influenza) during pregnancy was associated with autism spectrum disorders (ASD) and developmental delays; use of antipyretic medication attenuated the risk for ASD.[15] Additionally, prenatal fever was associated with mild motor coordination problems at age 7 years in a Danish study,[16] again suggesting some more subtle impact on neurodevelopment short of neural tube defects. Apart from congenital defects, maternal fever is believed to be associated with miscarriage early in pregnancy and with premature labor later in pregnancy.[17]

On January 9, 2015, FDA issued a Drug Safety Communication (DSC) regarding use of analgesics during pregnancy.[18] Among the observational studies described in that Drug Safety Communication was a study by Liew and colleagues finding an association between prenatal exposure to APAP and subsequent ADHD.[19] The DSC noted that FDA judged the findings from the Liew study and from two previous studies of this same association (by Streissguth and colleagues [20] and by Brandlistuen and colleagues[21]) to be inconclusive overall. Please refer to the May 15, 2014 DEPI 1 consult for a detailed review of these studies.

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With respect to biologic plausibility, Liew and colleagues speculated that the effect they observed might stem from endocrine disrupting properties of APAP. Other authors have speculated that APAP may have an impact on neurotransmitter systems, brain-derived neurotrophic factor, or the endocannabinoid system.[22] In terms of preclinical data, a recent study observed behavioral differences in adult mice following exposure to APAP in the neonatal period.[23]

2 REVIEW METHODS AND MATERIALS

This review discusses these recently published studies:

> Stergiakouli E, Thapar A, Davey Smith G. Association of Acetaminophen Use During Pregnancy With Behavioral Problems in Childhood: Evidence Against Confounding. JAMA Pediatr. 2016 Aug 15 [Epub ahead of print].
>
> Avella-Garcia CB, Julvez J, Fortuny J, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. Int J Epidemiol. 2016 Jun 28. [Epub ahead of print]
>
> Liew Z, Ritz B, Virk J, Arah OA, Olsen J. Prenatal Use of Acetaminophen and Child IQ: a Danish Cohort Study. Epidemiology. 2016 Jul 28. [Epub ahead of print]
>
> Vlenterie R, Wood ME, Brandlistuen RE, Roeleveld N, van Gelder MM, Nordeng H. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero: a propensity score matched cohort study. Int J Epidemiol. 2016 Aug 31. [Epub ahead of print]

3 REVIEW RESULTS

3.1 STERGIAKOULI ET AL.

- *Author, publication year and affiliation/funding*

This study was published online August 15, 2016. The authors are investigators with the Avon Longitudinal Study of Parents and Children (ALSPAC) in Bristol, England, which is funded by the U.K. Medical Research Council, the Wellcome Trust, and the University of Bristol.

- *Objectives*

The purpose was to assess the association between behavioral problems at age 7 years and maternal prenatal APAP use. For comparison, the study also assessed associations with maternal postnatal APAP use, and with partner's APAP use.

- *Design*

This was a prospective birth cohort study.

- *Methods: population source, study subject selection, study time period, IRB/OMB approval, patient consent if needed, outcome, exposure, sample size, statistical plan, etc*

Altogether, the ALSPAC study enrolled 14,541 pregnant women in Bristol, England, from April 1991 to December 1992. Of these, 7796 mothers and children provided data for this analysis. All participants provided informed consent and relevant ethics committees provided oversight. The outcome measure was the Strengths and Difficulties Questionnaire (SDQ)[24] obtained from the mother when the child was 7 years old. Cutoff scores distinguished children with or without behavioral problems in six behavioral domains; scores of 17 or higher met the cutoff for overall total behavioral difficulties, and of 7 or higher indicated hyperactivity. With respect to exposure, mothers reported their APAP use in the previous 3 months on questionnaires at weeks 18 and 32

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of pregnancy, and for comparison purposes, mothers and their partners reported their APAP use when the child was 61 months old. The statistical analysis applied generalized linear models with a log-link function and a Poisson distribution to estimate risk ratios for meeting the cutoff on a particular subscale of the SDQ; in other words, outcomes were defined by meeting or exceeding a specific value on the SDQ subscale. Covariates included maternal alcohol and tobacco use and psychiatric history, maternal reports of possible indications for APAP (i.e., infections, muscle and joint problems, migraine, or headache), and presence of selected ADHD "risk alleles" in mothers that had been genotyped. There did not appear to be an *a priori* primary outcome for the analysis, and the analysis did not account for other medication exposures during pregnancy.

- *Results*

Mean age was 29 years for mothers who both used or did not use APAP during pregnancy. Slightly more mothers who used APAP had a psychiatric illness (10% versus 7% for nonusers); also, smoking was more prevalent among APAP users (21% versus 17% for nonusers), as was alcohol use (60% versus 54% for nonusers). Five percent of children had some indication of behavioral problems according to the SDQ. The adjusted relative risk (95% CI) for SDQ total difficulties (score≥ 17) was nonsignificant for APAP use compared to no use at 18 weeks, and was 1.37 (1.07-1.75) for use at 32 weeks. The relative risk for SDQ hyperactivity scores ≥ 7 was 1.18 (1.01-1.38) for exposure at 18 weeks, and 1.22 (1.04-1.43) for exposure at 32 weeks. Also, there was a significantly elevated risk of conduct problems (score ≥4) with use at 32 weeks (risk ratio 1.35, 95% CI 1.13-1.60). The authors observed that associations were more prominent for late pregnancy APAP use. The analysis did not examine dose or duration of APAP use. There were no significant associations with maternal postnatal APAP use, though hyperactivity symptoms and conduct problems were significantly associated with partner's APAP use (data not shown). Adjusting risk estimates with prenatal APAP use for postnatal APAP use, or for partner's APAP use, did not materially change the risk estimates (data not shown). Maternal genotypes associated with ADHD did not appear to affect whether the mothers used APAP. Linear regression analysis of SDQ scores as continuous variables showed statistically significant positive beta coefficients for 32 week APAP use on all SDQ scales, except prosocial behavior. However, maternal postnatal APAP use was also associated with statistically significant, positive beta coefficients on 4 of 6 SDQ domains.

- *Strengths and limitations*

One of the strengths of the study was that APAP use during pregnancy was assessed prospectively, avoiding potential retrospective recall bias (in which mothers of affected children may be more apt to have thought about and to recall drug use during pregnancy). Assessment of the children at age 7 can be considered a strength, because behaviors at that age may be more stable than assessments of younger children. The SDQ is a recognized choice for a screening tool, having been validated against psychiatric assessments in a sample of 10,000 UK children. However, it showed better negative predictive values (roughly 95%) than positive predictive values (roughly 35%) for psychiatric diagnoses.[25] While minimizing false negatives at the expense of false positives is an appropriate balance for a screening instrument, it might present a limitation for research purposes. Overall, the study's reported prevalence of 5% for behavioral problems at age 7 seems reasonable, though the SDQ has shown greater sensitivity when completed by multiple informants,[26] rather than just one parent as in this study. Maternal reports of infections, muscle and joint problems, migraine, or headache were important covariates. Of these, infection may be the most likely to be a true confounder, as prenatal infections might be associated both with behavioral problems in the offspring, and with maternal APAP use. However, data on specific indications for APAP use were not available. The abstract of the manuscript cites unadjusted risk estimates, but only adjusted risk estimates are cited above. Other limitations include the apparent lack of a primary outcome measure, and uncertainty regarding the

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degree of correlation between SDQ scores and clinical psychiatric disorders. The association with partner's APAP use weakens the case for a direct causal relationship to prenatal APAP exposure. Exploring maternal genotype as a confounder was a novel approach, but did not extend to paternal genotype.

- *Conclusion*

On balance, this study provides modest evidence in favor of an association between prenatal APAP exposure and behavioral problems at age 7 years. Analyzing maternal or paternal APAP use at age 61 months for comparison only partially addresses the issue of confounding, since it is plausible that some conditions (e.g., fever) during pregnancy which prompted the mother to use APAP could also have affected fetal neurodevelopment, leading to confounding; adjusting for postnatal use of APAP would not necessarily account for this.

3.2 AVELLA-GARCIA ET AL.

- *Author, publication year and affiliation/funding*

This study was published June 28, 2016. The authors are affiliated with the Infancia y Medio Ambiente (INMA) project funded by a variety of grants, including grants from the Spanish Ministry of Health.

- *Objectives: primary & secondary*

The objective was to evaluate any adverse effects of prenatal APAP exposure on neurodevelopment, at ages 1 and 5 years.

- *Design*

This was a prospective birth cohort study.

- *Methods*

Mothers were eligible to participate in the INMA project if they were at least 16 years of age and were planning to give birth at a participating hospital in one of four regions of Spain. Ethics committees of each participating hospital provided approval. Multiple pregnancies were excluded. Recruitment took place in 2004-8; participation rates by region ranged from 45-68%. Outcome measures included the Bayley Scales of Infant Development (BSID) at age 15 months, and at age 5 years, the McCarthy Scales of Children's Abilities (measuring cognitive ability), the California Preschool Social Competence Scale (CPSCS), the Childhood Autism Spectrum Test (CAST), the Conners Kiddie Continuous Performance Test (K-CPT), and whether the child met Diagnostic and Statistical Manual (DSM-IV) criteria for ADHD. Exposure to APAP was determined during interviews of mothers at weeks 12 and 32 of pregnancy; all medications taken during pregnancy, or up to one month before pregnancy, and their indications, were reported; possible indications for APAP were analgesia, infection, or other. Outcome measures were analyzed as continuous variables (i.e., not with cutoff scores for outliers) using multivariable linear regression or negative binomial regression, adjusted for a variety of potential confounders, and results were expressed as incidence rate ratios (IRR). The investigators also analyzed APAP exposure according to whether it occurred in all 3 trimesters or not.

- *Results*

A total of 2195 children were assessed at 15 months, and 2001 at age 5 years; of the children in the sample at age 5, 41% had prenatal exposure to APAP. Analgesia accounted for 2/3 of the APAP indications; APAP users had more chronic illnesses, and were more likely to have smoked or had a fever during pregnancy. At 5 years of age, APAP exposed children showed more DSM-IV hyperactivity symptoms (adjusted IRR 1.41, 95% CI 1.01-1.98) but the association with total

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ADHD symptoms was nonsignificant. Other significant findings included significantly more detectability errors on the continuous performance task, and on the CAST measure of autistic symptoms, a statistically significant increase in males (beta= 0.63, 95% CI 0.09, 1.18) but a significantly lower rate of such symptoms among females (beta= -0.51, 95% CI -0.98, -0.05). In contrast, some continuous performance measures appeared to show greater deficits in exposed females than males, with a statistically significant p-value for gender interactions with "Commission" and "Detectability" mistakes. There was a correlation between autistic and ADHD symptoms (Spearman correlation 0.21, statistically significant), indicating that autistic symptoms and ADHD symptoms were present in the same child more often than if they occurred at random. Point estimates for DSM-IV ADHD symptoms were highest in the subgroup of 5-year olds exposed in all 3 trimesters, though the IRRs did not reach statistical significance within that subgroup. Similarly, the IRR for autistic symptoms was also highest in the subgroup of male 5-year olds exposed during all 3 trimesters. Excluding children whose mothers had indications of chronic illness, analgesia, or fever during pregnancy from the age 5 sample did not materially change the results; from the data in the online appendix, it appeared that only about 5% of the mothers who used APAP reported fever. Adjustment for maternal use of other medications was described as not affecting the results, though the data were not presented. Finally, there were no apparent effects on cognitive ability at age 15 months (Bayley) or 5 years (McCarthy), on motor development at age 15 months (Bayley), or on social competence scores at age 5 (CPSCS), in that the beta coefficients were non-significant.

- *Strengths and limitations*

Strengths of the study include prospective determination of exposure to avoid recall bias, and following up the exposed children at age 5 with a variety of neurodevelopmental assessments. Another important strength is that the mothers were asked to give the indication for APAP used during their pregnancy, permitting that to be accounted for in the analysis. The investigators reported significant trend tests for several outcomes across the 3 levels of exposure (none vs. use in 1 or 2trimesters vs. use in all 3 trimesters). Observing the greatest risks with exposure in all 3 trimesters could be interpreted as supporting the association, to the extent that neurodevelopment is a continuous process and not limited to the first trimester as is the case with other types of organogenesis.

Limitations include a lack of consistency of associations across the different behavioral evaluations, lack of details regarding cumulative APAP dose which limited the dose-response analysis, absence of assessments of clinical diagnoses as outcomes, and absence of an *a priori* primary outcome measure among the multiple assessments analyzed. The finding of an opposite effect on autistic symptoms in males (for whom prenatal APAP exposure increased risk) and females (for whom it was protective) is not readily explained and could be viewed as a limitation of the findings. However, the authors propose that neurodevelopment in males might be more sensitive to disruption; in fact one study of prenatal bisphenol A exposure and later behavioral problems found an association in boys but not girls.[27] However, the results on some of the continuous performance task measures seemed to indicate a greater susceptibility in females, which would be contrary to the hypothesis that males have more vulnerability.

- *Conclusions*

On balance, this study provides modest evidence for an association of prenatal APAP use with attentional problems, and with autistic behaviors, in exposed offspring at age 5.

3.3 LIEW ET AL.

- *Author, publication year and affiliation/funding*

Reference ID: 4299631

This study was published July 28, 2916. All authors are affiliated with the University of California, Los Angeles (UCLA). Funding was by the Danish Medical Research Council and the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

- *Objective*

The objective was to determine if prenatal APAP exposure affects IQ.

- *Design*

This was a population-based, prospective cohort study.

- *Methods*

Subjects were from a substudy of the Danish National Birth Cohort study entitled, "Lifestyle During Pregnancy Study." Women with children aged 5 years were selected for this substudy from September 2003-June 2008, with oversampling of women who used alcohol; the investigators adjusted for sampling and probability of agreeing to participate with inverse probability weights. Exposure to analgesics, including APAP use by week, was determined during telephone interviews at pregnancy weeks 12 and 30 and at age 6 months. Mothers also reported fever, infection/inflammation, or muscle/joint pain during the 30 week interview, though they did not report whether these were the specific indication for APAP use. Offspring with severe developmental delays were excluded. Psychologists administered the Weschler Primary and Preschool Scale of Intelligence-Revised (WPPSI-R) to assess IQ at age 5. The investigators used linear regression adjusted for multiple covariates (including alcohol and tobacco use during pregnancy, and maternal IQ), with the comparison group being mothers who reported no fevers or APAP use during their pregnancies. The investigators also analyzed IQ in relation to maternal aspirin or ibuprofen use. The UCLA Institutional Review Board and the Danish Data Protection Agency provided ethical oversight.

- *Results*

Results were available for 1,491 mothers and their 5 year old children. Mothers who used APAP were also slightly more likely to have used alcohol and tobacco, and were also somewhat more likely to have had the above-mentioned possible indications for APAP. Mean full scale IQ was 105.9 for unexposed and 103.9 for exposed children (after adjustment, a nonsignificant difference); there were no significant differences on mean verbal or performance IQs either. However, there was a significant adjusted mean difference in full scale IQ among children exposed during more than one trimester relative to unexposed children (mean difference -3.1, 95% CI -5.7, -0.45). Without APAP exposure, fever during pregnancy--but not the other two indications (muscle/joint disease or infection/inflammation)--was associated with a significant mean full scale IQ decrease (-4.1, 95% CI -7.3, -0.9). APAP exposure appeared to attenuate this effect somewhat, as shown in the figure below reproduced from the publication, though the confidence intervals around the point estimates were wide. There were no associations with prenatal aspirin or ibuprofen exposure, but the authors felt those comparisons had limited statistical power.

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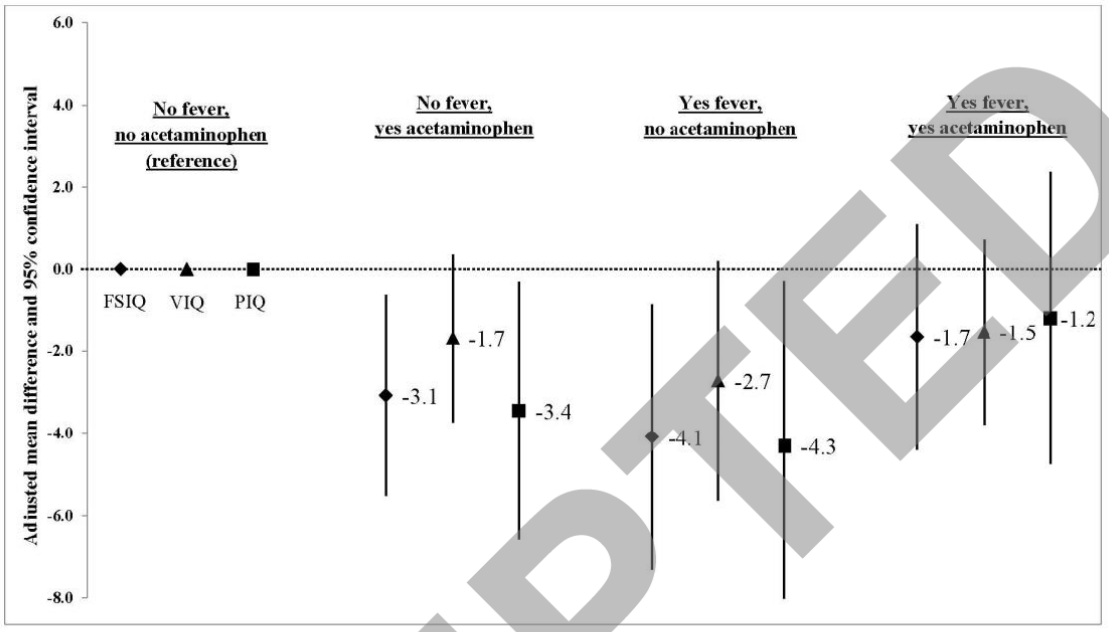

Figure1. Association between prenatal use of acetaminophen, maternal fever and child's full scale IQ (FSIQ), verbal IQ (VIQ), or performance IQ (PIQ). Mean differences and 95% CIs adjusted for parental education, maternal IQ, maternal smoking and drinking during pregnancy, parity, maternal age at child birth, child's sex, and prenatal use of ibuprofen or aspirin. Interaction p-values between acetaminophen and fever for FSIQ, VIQ and PIQ are 0.01, 0.13, and 0.02 respectively.

ACCEPTED

- *Strengths and limitations*

Strengths include use of cognitive assessments administered by psychologists, prospective determination of APAP use to avoid recall bias, and availability of data on possible confounders, including maternal fever during pregnancy. Limitations of the data include statistical imprecision, as evidenced by the width of the confidence intervals for many of the adjusted point estimates, and the fact that in the analysis of the full sample there was no significant relationship between prenatal APAP exposure and IQ. Another limitation is that while mothers reported the occurrence of potential indications for APAP including fever, musculoskeletal symptoms and inflammation, those who took APAP did not report the specific indication for which they were taking APAP. Although it is necessary to wait until the children are of sufficient age to perform IQ assessments, developmental influences over five years of childhood were not accounted for in the analysis. Also, it might have been of interest to have analyzed offspring with more severe developmental delays, but these were excluded.

- *Conclusions*

On balance, this study provides weak evidence for an association of lower IQ with prenatal APAP exposure in the absence of fever. It also provides evidence that maternal fever during pregnancy is associated with lower IQ, and the data suggest that APAP use for fever during pregnancy may mitigate the effect of fever on IQ, though the data lacked statistical power for a meaningful comparison.

3.4 VLENTERIE ET AL.

- *Author, publication year and affiliation/funding*

This study was published August 31, 2016. The Norwegian Mother and Child Cohort Study is funded by the Norwegian Ministry of Health and the US National Institutes of Health, among other sources.

Reference ID: 4299631

- *Objective*

The purpose of this study was to investigate neurodevelopmental problems following prenatal exposure to APAP in children at age 18 months.

- *Design*

This was a prospective cohort study using propensity score matching.

- *Methods*

Mothers who agreed to participate responded to questionnaires at gestational weeks 17 and 30, and at age 6, 18 and 36 months. Over 100,000 mothers were enrolled from 1999-2008, representing 41% participation. For the 18 month assessment, the sample size was 51,200. Children with major malformations were excluded. In utero exposures to APAP were ascertained from the week 17 and 30 and the 6 month questionnaires, including duration of use and information on possible indications of fever, pain and infection. Outcomes included the Ages and Stages Questionnaire (ASQ) assessing psychomotor milestones, the Emotionality, Activity and Shyness (EAS) questionnaire assessing temperament, and the Child Behavior Checklist (CBCL) assessing behavioral problems. To adjust for confounding, the investigators calculated propensity scores using 23 maternal characteristics (including reports during pregnancy of alcohol and tobacco use, depression, fever, infections, pain symptoms, and concomitant medications). The investigators created propensity score-matched cohorts for APAP exposure <28 days (n=13,503 matched pairs) and for APAP exposure 28+ days (n=1630 matched pairs).

- *Results*

Mothers using APAP tended to have more alcohol and tobacco use, had more depression and used more concomitant medications. The following table shows the unadjusted proportions of children with neurodevelopmental problems assessed at 18 months of age, from the total cohort (before propensity score matching), by exposure.

Outcome	% of children with 28+ days of prenatal APAP exposure (n=1787)	% of unexposed children (n=30,451)
Psychomotor problems	21.8%	19.7%
Behavioral problems	17.7%	14.7%
Temperamental problems	23.5%	23.6%

Propensity score matching achieved good balance on baseline characteristics. After matching, the only statistically significant odds ratio (OR) was for motor milestone problems (i.e., delayed walking), for which the OR was 1.35 (95% CI 1.07-1.70) with 28+ days of exposure. The OR for communication problems approached statistical significance (1.38, 95% CI 0.98-1.95). In the full sample, there were statistically significant crude ORs for fine motor problems (OR 1.17, 95% CI 1.01-1.36, number needed to harm 39), communication problems (OR 1.32, 95% CI 1.05-1.66, number needed to harm 67), and externalizing behaviors (OR 1.50, 95% CI 1.26-1.76, number needed to harm 28). In sensitivity (or subgroup) analyses limited to mothers with headache, fever or infections, results were similar though they had less statistical precision. There were no associations with use of APAP less than 28 days.

- *Strengths and limitations*

Strengths of the study included prospectively collected information on exposure and possible indications for APAP use. However, the study has several limitations. There was no *a priori* primary outcome measure among the various assessments made of the children, so the analysis

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was vulnerable to problems from multiplicity of testing; in other words, the multiplicity of outcomes increased the chance of Type 1 error. On the other hand, the propensity score matched sample may not have been large enough to provide sufficient statistical power. The fact that roughly 1/5 of children were identified as having some neurodevelopmental problem suggests that the outcome measures may have provided sensitivity at the expense of specificity, and make the outcomes more difficult to interpret (i.e., children in the top quintile on these measures were considered to have an outcome). Another limitation is the use of neurodevelopmental assessments at age 18 months; most child psychiatric disorders present at older ages.

- *Conclusions*

This study provides weak evidence for delayed motor development (delayed walking) being associated with in utero APAP exposure. Between this analysis at age 18 months and the previously published analysis from the same cohort showing associations with neurodevelopmental outcomes at 3 years (Brandlistuen 2013, in Appendix Table), the previously published data on the 3 year old children are likely to be more meaningful.

4 DISCUSSION

Altogether, 8 observational studies conducted in 6 prospective pregnancy cohorts have examined neurodevelopmental outcomes following prenatal APAP exposure, and 7 showed some association with adverse neurodevelopmental outcomes (please see the Appendix Table for a summary of these studies, along with a study by Zerbo et al. of prenatal antipyretic use, described below). The one study which found no associations with prenatal APAP exposure (Streissguth et al., 1987) had the smallest sample (421 mothers), but nonetheless did report associations with prenatal aspirin exposure (perhaps suggesting a comparatively greater risk from aspirin). The following tables summarize the findings by particular outcomes. Statistically significant findings are highlighted. On balance, though the results by particular outcomes vary across studies, as seen below, evidence is accumulating that there is a reproducible association of prenatal APAP exposure with adverse neurodevelopmental outcomes. The question, of course, is whether it is a causal association.

Cognitive development

Study	Outcome	Finding for prenatal APAP exposure versus unexposed
Avella-Garcia 2016	IQ	No significant association
Liew 2016	IQ	Mean -3.4 points in absence of maternal fever
Streissguth 1987	IQ	No significant association (aspirin associated with lower IQ)

Attention problems

Study	Outcome	Finding for prenatal APAP exposure versus unexposed
Avella-Garcia 2016	ADHD symptoms	Increased risk
	Continuous performance task	Increased errors
Liew 2014	Diagnosis of Hyperkinetic Disorder	Increased risk (HR 1.4, 95% CI 1.2-1.6)
	Use of ADHD drugs	Increased risk (HR 1.3, 95% CI 1.2-1.4)

Stergiakouli 2016	SDQ hyperactivity score 7+	Increased risk (HR 1.2, 95% CI 1.0-1.4)
Streissguth 1987	Video vigilance task	No association (aspirin exposure associated with more errors)
Thompson 2014	Conners scale	Elevated subscales, but not elevated overall ADHD index

Motor development

Study	Outcome	Finding for prenatal APAP exposure versus unexposed
Avella-Garcia 2016	Bayley aged 15 mos. and McCarthy aged 5 yrs.	No associations
Brandlistuen 2013	Motor milestones age 3	Significantly more psychomotor problems
Vlenterie 2016	Walking at 18 months	Delayed

Autistic behaviors

Study	Outcome	Finding for prenatal APAP exposure versus unexposed
Avella-Garcia 2016	Childhood Autism Spectrum Test	In males, dose-related increase in reported autistic signs/symptoms; in females fewer symptoms
Zerbo 2013	Case-control study of autistic spectrum disorders	Maternal fever associated with autistic spectrum disorders, antipyretic use attenuated association

General behavioral problems

Study	Outcome	Finding for prenatal APAP exposure versus unexposed
Brandlistuen 2013	Child Behavior Checklist age 3	Increased behavior problems
Liew 2014	Strengths and Difficulties Questionnaire age 7	Increased risk of high “Total Difficulties” score
Stergiakouli 2016	Strengths and Difficulties Questionnaire age 7	Increased risk of high “Total Difficulties” score (later pregnancy exposure)
Thompson 2014	Strengths and Difficulties Questionnaire ages 7, 11	Increased scores

All studies reviewed made some adjustments for potential confounders in their analyses, which is a desirable design feature. However, a generic limitation of the efforts to account for potential confounders is that we do not fully understand all the causal factors for these various neuropsychiatric outcomes. Another generic limitation of these studies is the inability to account for developmental influences during the early childhood years, to the extent these may have differed between APAP exposed and unexposed children. The Brandlistuen study had a particular strength in this respect, however, since investigators assessed outcomes in siblings who were discordant for prenatal APAP exposure, which should have controlled for many environmental and familial factors shared by siblings. Another design feature of the Brandlistuen study that

helped address confounding was the analysis of ibuprofen prenatal exposures, for which there were no significant associations (though motor milestone delays showed p-values < 0.10).

There was not a clear pattern across studies suggesting exposure during a particular gestational age was more likely to show an association, but of course neurodevelopment proceeds throughout the pregnancy, unlike organogenesis of other major organs.

Another common limitation among these studies was lack of details regarding dose and duration of APAP use by the mothers. This is often a limitation of studies of over-the-counter drug exposures, for which pharmacy or clinical records are not useful. However, any misclassification or "noise" in the exposure data would be expected to make associations more difficult to find, rather than to produce spurious associations. Despite the challenges in documenting the level of APAP exposure, several studies showed some evidence of higher risk with longer duration of exposurefor neurodevelopmental measures (Avella-Garcia 2016, Brandlistuen 2013, Vlenterie 2016, Liew 2014).

The relative risk estimates in these studies are not large in magnitude (less than 2) which one could argue makes confounding a plausible explanation from a quantitative standpoint. However, as a benchmark, Vlenterie and colleagues point out that effect sizes observed in neurodevelopmental measures with prenatal lead exposure are on the order of 0.25 (of a standard deviation), similar to the effects of APAP seen in the Norwegian Mother and Child Cohort (see Brandlistuen 2013, in Appendix Table).

Publication bias may be considered as a possible explanation for the fact that a large majority of publications report some positive association. However, Thompson et al. undertook their analysis of ADHD data from the Auckland Birthweight Collaborative Study specifically in response to the publication by Liew and colleagues in 2014; presumably, they would have published their findings regardless of whether they reproduced the association with ADHD or not; furthermore, the journal PLOS One where the article by Thompson et al. appeared accepts 69% of submissions.[28]

A pharmacology-toxicology consultation for TSI 1355 by Dr. D. Charles Thompson on February 8, 2016 noted that there are currently no established animal models for ADHD in children, and accordingly there would be no obvious means to gather useful preclinical data to assist in evaluating the reported association between in utero APAP exposure and ADHD. However, the additional literature moves the focus away from ADHD specifically, towards a broader spectrum of behavioral and cognitive neurodevelopmental outcomes. Perhaps some of these might be represented by valid animal models that could provide experimental insight into biological plausibility.

Another recent study deserves mention here, though it considered only prenatal use of antipyretics in general and not APAP specifically. Zerbo and colleagues conducted a case-control study of children aged 2-5 years with either autistic spectrum disorders or developmental delay, to determine if there was an association with fever or influenza during pregnancy; they also collected data on anti-pyretic use, finding that fever during pregnancy was associated with both autistic spectrum disorders and developmental delay, but that the association was attenuated (to the point of being nonsignificant) when the mothers reported use of antipyretics. For developmental delay, the OR was still elevated for fever with anti-pyretic medication though the point estimate was lower (see Appendix Table).[29] One weakness of the study is that the exposure was determined retrospectively, so there could have been some recall bias, though it is not clear how that would have influenced the apparent interaction between fevers and antipyretics.

Maternal fever appears to be a confounder in that it is associated both with adverse neurodevelopmental outcomes, and with maternal use of APAP during pregnancy. Many of the

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studies reviewed had data on maternal fever as a covariate (Avella-Garcia 2016, Brandlistuen 2013, Liew 2014, Thompson 2014, Vlenterie 2016). Nonetheless, the aforementioned results regarding maternal fever from the study by Zerbo and colleagues and the Liew 2016 publication, raise a more complex possibility, namely, that while maternal fever is a likely confounder, APAP use may attenuate the risk from fever. Logically, this hypothesized protective effect in the setting of fever, presumably on the basis of APAP's antipyretic effect, is not mutually exclusive with the APAP being a neurodevelopmental toxin per se.

While APAP, which is generally perceived to be safe during pregnancy, does not carry the risks of aspirin or NSAIDs, more nuanced advice about its use during pregnancy seems appropriate now, in view of these emerging data on neurodevelopmental outcomes.

5 CONCLUSIONS

In the studies reviewed, in utero exposure to APAP was associated with a spectrum of adverse neurodevelopmental outcomes, though findings with respect to specific outcomes varied somewhat across studies, and positive findings were generally modest. While this association appears reproducible, a causal relationship is not certain because of the possibility of confounding, particularly by conditions such as maternal fever and infection that may prompt pregnant women to take APAP but which may also be risk factors for neurocognitive problems. That said, all of the studies which reported an association employed strategies to minimize such confounding, and one study failed to find an association with prenatal ibuprofen. Additionally, data from two studies suggest that APAP (or antipyretics in general) might mitigate adverse neurodevelopmental effects of maternal fever.

6 RECOMMENDATIONS

With growing evidence for adverse neurodevelopmental outcomes associated with in utero APAP exposure, even in the absence of proof of a causal relationship, we recommend DNDP once again bring this issue to the attention of consumers and health care providers through one of the communication avenues available to the agency. The essential points to communicate would be that current data raise the possibility of neurodevelopmental harm to the fetus from maternal APAP use, that accordingly it should be used judiciously during pregnancy, that other analgesics are associated with more definite pregnancy risks, and that APAP may be needed as an antipyretic to reduce risks of maternal fever.

With respect to further evaluation of this signal, it may be beneficial to re-consult Pharmacology/Toxicology to ask whether any preclinical models might address any of the expanded spectrum of neurodevelopmental outcomes that have now been reportedly associated with prenatal APAP exposure.

If additional observational studies are undertaken, it would be desirable to have them examine whether APAP modifies the effect of maternal fever or infection (rather than simply adjusting for fever or infection as confounders), and perhaps account for confounders during early childhood to the extent that is feasible. However, identifying a database that can address these issues may be challenging.

APPENDIX TABLE. STUDIES OF NEURODEVELOPMENTAL OUTCOMES FOLLOWING IN UTERO ACETAMINOPHEN EXPOSURE

Study	Objectives/Aims/Scope	Design	Data Source	Subject selection criteria	Exposure	Outcome(s)	Sample Size	Statistical Analyses	Study Results
Avella-Garcia 2016	To determine if prentatal APAP exposure adversely affects neurodevelopment at 1 and 5 years of age	Longitudinal, prospective birth cohort study	Infancia y Medio Ambiente project in 3 regions of Spain, 2004-8	Mothers eligible if 16+ years old, carrying singleton pregnancy, & planning to give birth at participating hospital	Medications (including APAP) used during pregnancy or 1 mo. before determined by interview at pregnancy weeks 12 and 32. Exposures after week 32 interview not ascertained.	Bayley scale of infant development at age 15 months. McCarthy IQ scale, CPSCS, CAST, DSM-IV criteria for ADHD, Conners K-CPT at age 5	2195 children age 1 yr, 2001 children age 5 yrs	Multivariable linear regression or negative binomial regression; outcomes were continous variables. Multiple covariates evaluated including chronic illness, fever, UTI.	After adjustment, APAP exposure associated with significantly more hyperactivity/impulsivity ADHD symtpoms, K-CPT commission errors, and in males only, autistic symptoms. No significant effects on cognitive measures, social competence scale scores. Suggestion of increased risks with greater frequency of use.
Brandlist-uen 2013	To examine psychomotor, behavioral and temperament outcomes with prenatal APAP exposure at age 3 yrs	Population-based prospective cohort study	Norwegian Mother and Child Cohort Study, 1999-2008	Mothers from anywhere in Norway recruited into cohort at time of their gestational week 17 ultrasound. This analysis limited to same gender sibling pairs	APAP exposure, frequency, indication ascertained by questionairres (at 17 wks and 30 wks gestation, and 6 mos postnatal. Ibuprofen exposure similarly ascertained as comparator	ASQ for psychomotor development, CBCL for behavioral problems, EAS for temperament	2919 same-sex sibling pairs, of whom 939 were discordant for prenatal APAP exposure. 155 discorda	Generalized linear regression to calculate beta coefficients. Data on fever, infection, concomitant exposures assessed for inclusion in model.	APAP exposure of 28+ days associated with delayed gross motor development, delayed communication, externalizing and internalizing behaviors, higher activity. No statistically significant effects of ibuprofen exposure, though motor milestones

Study	Objectives/Aims/Scope	Design	Data Source	Subject selection criteria	Exposure	Outcome(s)	Sample Size	Statistical Analyses	Study Results
							nt sibling pairs for ibuprofen exposure .		showed p-values <0.10.
Liew 2014	To evaluate whether prenatal APAP exposure increases the risk of ADHD	Population-based prospective cohort study	Danish National Birth Cohort, 1996-2002	Danish-speaking mothers of singleton infants who responded to 3 phone interviews (at 12 and 30 wks gestational age and 6 mos postpartum)	Use of APAP and other painkillers by gestational week reported during telephone interviews (at 12 and 30 wks gestational age and 6 mos postpartum)	At age 7: prescriptions for ADHD drugs, diagnoses of Hyperkinetic Disorder, SDQ	N=64322 for diagnosis and ADHD drug use; 40916 of these with SDQ data	Cox proportional hazards regression for ADHD outcomes; generalized linear models for SDQ. Covariates incl. maternal infection/inflammation, fever, musculoskeletal disease, smoking, maternal mental health, childhood behavior problems of parents. Reference=children w/o prenatal exposure	At age 7, for hospital diagnosis of HKD, HR = 1.37, 1.19-1.59, for use of ADHD medications, HR = 1.29, 1.15-1.44; for SDQ total difficulties score of 17+, RR=1.13 (1.01-1.27). Evidence for exposure-response trend.

Study	Objectives/Aims/Scope	Design	Data Source	Subject selection criteria	Exposure	Outcome(s)	Sample Size	Statistical Analyses	Study Results
Liew 2016	To examine whether prenatal use of APAP affects offspring's IQ	Population-based prospective cohort study	Danish National Birth Cohort, 1996-2002	"Lifestyle During Pregnancy Study" of women selelcted from the Danish National Birth Cohort, with children 5 years old, Sep 2003-Jun 2008, oversampled for EtOH use	Use of APAP and other painkillers by gestational week reported during telephone interviews (at 12 and 30 wks gestational age and 6 mos postpartum). Fever, infection/inflammation, muscle/joint pain determined at 30 wks	IQ (on WPPSI-Revised version)	1491 mothers and children	Linear regresssion adjusted for maternal IQ and other covariates. Reference = mothers with no fevers or APAP during pregancy	Children of mothers who used APAP during pregnancy and did not have fever had performance IQs lower by 3.4 (0.30-6.6) points on avg; fever without APAP lowered both verbal and performance IQ, but no significant effect of APAP in mothers who had fever
Stergiak-ouli et al. 2016	To examine associations between behavioral problems and prenatal APAP exposure	Longitudinal, prospective birth cohort study	Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2, Bristol, UK	Any pregnant woman from the study region with due date between April 1, 1991 and December 31, 1992	Prenatal APAP exposure assessed by questionnaire, at 18 and 32 weeks of gestation and when child was age 61 months	SDQ at age 7 years	7796 mothers	Generalized linear models to estimate risk ratios adjusted for multiple covariates, including maternal EtOH and tobacco use, psychiatric history, infections, musculoskeletal symptoms, migraine, headache.	RR for SDQ total difficulties (score≥ 17): NS at 18 wks, 1.37 (1.07-1.75) at 32 wks. RR for SDQ hyperactivity score ≥ 7: 1.18 (1.01-1.38) for exposure at 18 wks, 1.22 (1.04-1.43) for exposure at 32 wks.
Streiss-guth et al. 1987	To provide an exploratory analysis of neurodevelopmental teratogenicity of APAP and ASA	Logintudinal prospective pregnancy cohort study	Seattle Longitudinal Prospective Study on Alcohol and Pregnancy, 1974-5	Consecutive pregnant women receiving prenatal care	—Prenatal use of ASA and APAP assessed at month 5 by maternal interview	IQ (WPPSI) and video vigilance task	421 children assessed at 4 yrs, 3 mos	Multiple regression, including maternal alcohol, nicotine, caffeine, and antibiotic use, and various covariates that affect IQ	—ASA exposure negatively correlated with IQ and with errors on vigilance task. No correlations with APAP exposure.

Study	Objectives/Aims/Scope	Design	Data Source	Subject selection criteria	Exposure	Outcome(s)	Sample Size	Statistical Analyses	Study Results
Thompson et al. 2014	To assess the reported association between prenatal exposure to APAP and ADHD.	Longitudinal cohort study	Aukland Birthweight Collaborative Study of children born Oct 1995- Nov 1997	In the catchment area, all small for gestational age (SGA) infants (in the tenth percentile) and an approximately equal number of other fullterm infants selected randomly	Prenatal exposure to APAP (yes/no), as reported by mothers during interview shortly after birth	SDQ and Conners Behavior Rating Scale, at 7 and 11 years of age	N=614 for SDQ, N=617 for Conners	Multivariable general logistics model for difference in scores, multiple risk factors for ADHD as covariates, including maternal smoking, alcohol use, high fever, psychiatric history	Statistically significantly higher adjusted Total Difficulties scores on SDQ for APAP-exposed children. Elevations on certain subscales of Conners but not on ADHD index.
Vlenterie 2016	To investigate neurodevelop-mental problems following prenatal exposure to APAP in children age 18 mos.	Prospective cohort study	Norwegian Mother and Child Cohort Study, 1999-2008	Mothers from anywhere in Norway recruited into cohort at time of their gestational week 17 ultrasound.	APAP exposure, frequency, indication ascertained by questionairres (at 17 wks and 30 wks gestation, and 6 mos postnatal.	ASQ, EAS and CBCL, age 18 mos.	1630 propensity score matched pairs (28+ days of APAP vs. no APAP)	Propensity score matched OR	Delayed motor milestone (walking) OR 1.35 (1.07-1.70) with 28+ days prenatal APAP exposure, otherwise no significant associations
Zerbo 2013	To assess associations between maternal influenza and fever during pregnancy and autism or developmental delay.	Population-based case-control study	Childhood Autism Risk from Genetics and Environment (CHARGE) study in 20 California counties, Jan 2003-Sep 2010	Cases = children aged 2-5 years with autism, autism spectrum disorders (ASD), or developmental delay (DD) without ASD. Controls randomly selected from state birth files, matched on age and region, with oversampling of males	Occurrence of fever and use of antipyretics during pregnancy determined retrospectively from telephone interview. Antipyretics included nonsteroidal anti-inflammatory drugs	Not applicable (case-control design)	538 ASD cases, 163 DD cases, 421 controls	Multivariate analyses weighted by probability by participating in the study based on selected covariates	Weighted OR for ASD with fever and no anti-pyretic medication, 2.55 (1.30-4.99), with fever but using antipyretic medication, 1.30 (0.59-2.84). Weighted OR for DD with fever and no anti-pyretic, 2.73 (1.19-6.28), with fever plus antipyretic, 2.05 (0.78-5.36).

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